SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS LINK GENE RESPONSIBLE FOR HEREDITARY NERVE DISEASE TO CARDIOVASCULAR PROBLEMS

DALLAS – Dec. 20, 2002 – While studying a gene that can cause tumors in the nervous system, UT Southwestern Medical Center at Dallas researchers found the gene's absence in certain blood vessel cells also can trigger cardiovascular problems such as hypertension and congenital heart disease.

"This study demonstrates that our previous notions about this gene's primary function in the heart was wrong. This is a really surprising finding," said Dr. Yuan Zhu, instructor in the Center for Developmental Biology and molecular biology and lead author of the study published in the January issue of *Nature Genetics*. An early version is listed online at the journal's Web site.

Zhu and the other researchers believe their latest findings may result in new therapeutics for the hereditary disease neurofibromatosis, as well as advances in the treatment of cardiovascular problems. They made their discovery while investigating the cardiac neural crest – the part of the embryo that eventually forms the nervous system – in mice.

Neurofibromatosis, also known as von Recklinghausen disease, is a disorder of the gene *Nf1* that causes tumors to form on the nerves, skin and internal organs. People normally have two "good" copies of this tumor-suppressant gene, but those with the disease have one "good" and one "bad," or mutant, copy of the gene.

Researchers found the gene lacking in endothelial cells, which make up the inside of blood vessels and serve several functions. The cells come from large and small veins and arteries, capillaries, or specialized vascular areas such as the umbilical vein of newborns, blood vessels in the brain or vascularized solid tumors.

There are two distinct forms of neurofibromatosis. One form is NF-1, which affects multiple organ systems and is present in about one in every 4,000 people worldwide. The benign tumors, called neurofibromas, develop into malignant tumors, called neurofibrosarcomas, in 10 percent to 15 percent of NF-1 patients. The malignant tumors do not respond well to currently available treatments.

Studies in mice had suggested that NF-1 patients also might suffer from cardiovascular diseases, which was not previously noticed. As the major manifestations of NF-1 are in cells

(MORE)

derived from cells in the neural crest (the part of the embryo that eventually forms the nervous system), it was believed NF-1-related cardiovascular abnormalities result from abnormal development of the cardiac neural crest.

In the *Nature Genetics* study, Zhu first inactivated the *Nf1* gene in the neural crest cells in mice in order to generate a tumor model similar to human neurofibromatosis. Surprisingly, the mice did not survive after birth, leading the researchers to collaborate with the University of Pennsylvania Health System in studying the heart for answers.

"At the beginning of this effort, my goal was not to study the heart," said Zhu, who has been studying neurofibromatosis since 1995.

In follow-up research, the *Nf1* gene was inactivated in three different heart cells – neural crest, endothelial and muscle – to further understand why the mice died. This time, the mice did not develop heart abnormalities when the gene was removed in either the neural crest or muscle cells. The mutated mice with *Nf1* inactivation in the endothelial cells have abnormal heart development similar to *Nf1* knockout mice, which lack *Nf1* function in every cell. These tests showed the NF-1-related cardiovascular diseases result from loss of *Nf1* in endothelial cells, not in neural crest cells as first thought.

Dr. Luis Parada, director of the Center for Developmental Biology and senior author of the study, said making the endothelial cell connection explains why previous attempts to create a mouse model for NF-1, thought to be a crucial step in understanding and treating neurofibromatosis, have failed.

"This is a particularly poignant example of how by using mice models to study human disease, we not only can recapitulate the disease with great fidelity but also learn things about the disease that were not evident and might never have been evident by studying patients," said Parada, director of the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration.

Research for the *Nature Genetics* study was supported by grants from the National Institutes of Health, U.S. National Institute of Neurological Disorders and Stroke, the U.S. Department of Defense, W.W. Smith Foundation, and the American Heart Association. Zhu also received funding as a 2001-2002 winner of a Young Investigator Award from the National Neurofibromatosis Foundation.

Researchers from the Children's Hospital of Philadelphia and Kumamoto University School of Medicine in Japan also collaborated in the study.